REMARKS

The Interview of 8 June 2009

Applicants and the undersigned thank the Examiner and his Supervisor for their courtesy during the in-person interview of 8 June 2009. In accordance with MPEP §713.04, a summary of the substance of the interview is provided herein and is incorporated in the comments below.

The Cited Art Does not Render the Claimed Invention Obvious

The sole rejection is an obviousness rejection, wherein the Office Action of 11 March 2009 rejected claims 23 and 27-49 under 35 U.S.C. §103 as allegedly being unpatentable over Marler, in view of Bent, Agerup, Vanderhoff, The Merck Index and Hawley's Chemical Dictionary. The crux of the rejection is that the molecular weight of the alginate used in the methods would be obvious to one of skill in the art in view of the cited references. It is Applicants' position that the cited references can not support a *prima facie* case of obviousness, because the cited references fail to teach or suggest the claimed molecular weight of alginate. Accordingly, Applicants respectfully disagree with the Office Action and assert that the claims are not obvious in view of the cited art.

As was discussed in previous responses and at the interview, none of the cited references teach or suggest the use of alginate with the specified molecular weight. During the June 8th interview the undersigned pointed out that all the claims recite the element that the alginate used in the methods must have a molecular weight of between about 100kDa and about 1200kDa, prior to cross-linking. Accordingly, the cited references must teach or suggest the claimed range of alginates to render the invention obvious. The Examiner and his Supervisor agreed that none of the cited references teach or suggest the claimed range of alginate. Applicants assert, therefore, that the cited references can not, by law, render the claimed invention obvious.

To account for this lack of disclosure amongst the cited references, the March 11th Office Action states that "[i]t is well within the skill level of the artisan to adjust … the molecular weight of the alginate in order to obtain maximum beneficial effects." *Office Action of 11 March*

2009, page 6. Thus, as done in previous rejections, the Office Action is filling in the missing elements by asserting that routine optimization is all that is required to render the invention obvious in view of the cited art.

Again, Applicants disagree. To establish a *prima facie* case of obviousness by asserting routine optimization of a variable, the prior art must recognize the optimized variable as a result-effective variable. Moreover, Applicants assert that more is required from the Office to establish obviousness than just a mere assertion that something is "routine optimization." Indeed, the MPEP states that "[a] particular parameter must first be recognized as a result-effective variable, *i.e.,* a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." MPEP §2144.05 (emphasis added) (citing *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977)). Applicants assert that the Examiner has not established that the molecular weight of the alginate used in the cited art methods is recognized as a result-effective variable.

The alginate used in the methods of the claimed invention should possess long-term stability and be injectable for increasing tissue volume. The methods require injection of the material. Given that the material is being injected, it is ideal that the material be stable over a period of time in order to ensure that long-term aesthetic effects are achieved. Again, because the alginate is being injected, the material should be highly pure and possess low level toxicity. The purified inventive material with the given molecular weight indeed exhibits significantly improved properties (in particular long term stability) as compared to the alginate material used in the methods disclosed in the cited art. None of the references, however, teach that increasing the molecular weight of alginate would be effective to increase its stability and/or decrease its toxicity. Marler, Bent and Vanderhoff only disclose commonly used, low molecular weight alginate, and none of the references teach or suggest augmenting the molecular weight of the alginate because the molecular weight of the alginate is a result-dependent variable.

The cited prior art methods that try to provide highly purified alginate never provide an alginate with a molecular weight of more than 100kDa. Instead the cited references only provide

for a much lower molecular weight alginate. Moreover, the state of the art at the time of filing actually refers to the mannuron/guluron acid ratio of alginate material as the determining parameter for its *in vivo* stability thereby ignoring the molecular weight of the alginate. For example, Mancini *et al,* which is appended to this response, explored *in vivo* characteristics, including stability, and focused primarily on the mannuron/guluron ratio and completely ignores the relevance of the molecular weight of the alginate. Thus, the only thing that the cited art could possibly motivate one to optimize would be the mannuron/guluron acid ratio of the alginate material in an attempt to increase the long-term stability of the implant. Nothing in the cited art suggests that the molecular weight of the alginate would be crucial for increasing the stability.

In short, the Office has failed to establish that the claimed invention is obvious because the cited references do not teach all the limitations of the claimed invention and the cited art does not recognize the molecular weight of alginate as a result dependent variable. As discussed at the interview, Applicants' position is fortified by *Ex parte Whalen*, 89 USPQ2d 1078 (Bd. Pat. App. & Int. 2008), a recent precedential decision of the Board of Patent Appeals and Interferences (BPAI), a copy of which was provided to the Examiner and his Supervisor. The facts in *Whalen* are remarkably similar to those of the present application, and the Board agreed with applicants that the Office had not established a case of *prima facie* obviousness.

In *Whalen*, the examiner rejected claims for embolizing an aneurysm at a vascular site comprising the use of a biocompatible polymer, where the biocompatible polymer had a "molecular weight sufficient to impart … a viscosity of at least about 150 cSt … ." *Ex parte Whalen,* 89 USPQ2d at 1079. The examiner in *Whalen* cited three prior art documents (Evans, Greff '767 and Taki), but none of the references recited a viscosity limitation of the polymer. To fill in this missing requirement, the examiner asserted that "a person of ordinary skill in the art 'would have been motivated to optimize the viscosity of the Evans' … final formulations, because he would have had a reasonable expectation of success in achieving the safest clinical outcome … ." *Ex parte Whalen,* 89 USPQ2d at 1083.

In addressing this obviousness rejection, the Board stated that

> [t]he Examiner has not made out a prima facie case that the claimed compositions would have been obvious based on the teachings of Evans, Greff '767, or Taki. While 'the discovery of an optimum value of a variable in a known process is normally obvious,' *In re Antonie,* 559 F.2d 618, 620 [195 USPQ 6] (CCPA 1977), this is not always the case. One exception to the rule is where the parameter optimized was not recognized in the prior art as one that would affect the results. *Id.*
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> Here, the Examiner has not pointed to any teaching in the cited references, or provided any explanation based on scientific reasoning, that would support the conclusion that those skilled in the art would have considered it obvious to 'optimize' the prior art compositions by increasing their viscosity to the level recited in the claims. No reason to have done so is apparent to us based on the record. On the contrary, the references all suggest that low viscosity was a desired property in embolic compositions. …
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> …
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> Thus, the references teach that low viscosity is a desirable characteristic for embolic compositions. In our view, none of the cited references would have led a person of ordinary skill in the art to modify the known embolic compositions by increasing their viscosity to at least 150 cSt at 40°C. The Examiner has not adequately explained why such a modification would have been obvious.

Ex parte Whalen, 89 USPQ2d at 1083-1084 (emphasis added). It is noteworthy that the Board actually *reversed* the examiner to reach a conclusion of non-obviousness, based on the facts before it.

Moreover, Applicants reiterate that the claims require ionic cross-linkage and at least one cited reference, Vanderhoff, explicitly emphasizes that covalent cross-linking is strongly preferred and, in fact, discourages the reader from using ionic crosslinking. Indeed, Vanderhoff discusses using calcium ions to cross-link the alginate, but that "ionic bonds may be broken down by a change in external conditions, *e.g.,* by chelating agents. On the other hand, covalent bonds are stable in the presence of chelating agents. Thus, the most preferred cross linking agent

for use in the practice of the invention is one that forms covalent bonds … rather than ionic bonds." Vanderhoff, page 9, lines 30 – page 10, line 4. Thus, the Examiner's own reference teaches away from the ionic bonds used in the claimed methods.

Applicants highlight this passage in Vanderhoff because the Board in *Whalen* also discussed a proper obviousness analysis when a reference teaches away from a claimed invention. Indeed, the *Whalen* Board, in view of the Supreme Court's *KSR* decision, stated that

> … when the prior art teaches away from the claimed solution as presented here …, obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition.

Ex parte Whalen, 89 USPQ2d at 1084.

To be clear, the cited art[1] does not even hint, let alone suggest or teach, the use of the inventive alginate material with a molecular weight of 100kDa – 1200kDa that is ionically crosslinked. Accordingly, Applicants assert that the references, alone or in combination, do not teach injection of cationic cross-linked alginate to increase tissue volume. In fact, as discussed in previous responses, all of which are incorporated by reference, the combination of cited art would, at best, result in a low molecular weight alginate that is covalently crosslinked and possess a myriad of stability and toxicity issues. Nothing in the art would direct, guide or motivate one of skill in the art to (a) increase the molecular weight of the alginate and (b) use ionic crosslinking procedures to arrive at the claimed invention. Moreover, based on Vanderhoff's disclosure alone, one of skill would not have an *a priori* reasonable expectation of

[1] Agerup, which is also cited against the present claims, also fails to cure the deficiencies of the cited art of record. Agerup is completely different from the subject matter currently claimed, since Agerup uses dextranomeric microbeads for tissue augmentation, as the Office Action establishes. Furthermore, Agerup fails to teach the use of high molecular weight alginate, even as a carrier for the dextranomer.

success in using ionically crosslinked alginate. Thus, the references can not be combined to render obvious the presently claimed invention.

Moreover, there is no reason of record as to why one of skill in the art would "optimize" the molecular weight parameter or choose ionic binding over covalent bonding, in light of Vanderhoff teaching away from using ionic methods. In addition, in view of the Board's decision in *Whalen*, Applicants assert that the claimed invention must be considered non-obvious. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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